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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BASI, NIRMAL SINGH	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/518,381	LI ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *10 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-96* is/are pending in the application.

4a) Of the above claim(s) *30, 32, 40, 42, 50, 52, 62, 64, 74, 76, 82, 84-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *23-29,31,33-39,41,43-49,51,53-61,65-73,75,77-81 and 83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Amendments filed 4/10/04 and 1/10/02 have been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action (10/10/01).

3. **Objections**

The disclosure remains objected to because of the following informalities:

Applicants are required to use the heading "Brief Description of the Drawings" to describe the drawings. See MPEP 608.01(f). Applicant states page 5 states "Brief Description of the Figures". The specification must be amended to "Brief Description of the Drawings" as required by MPEP 608.01(f) to over come the objection.

Appropriate correction is required.

4. ***Claim Rejection, 35 U.S.C. 112, Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 57, 69, 77, 78-81 and 83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 77 remains indefinite because it is not clear which amino acids comprise the transmembrane domain of SEQ ID NO: 4 so as to allow the metes and bounds of the claims to be determined. Applicants argue the specification teaches that the transmembrane regions of G-protein coupled receptors, such as

EDG-1-1ike protein are generally designated as TMI-TM7; and that each transmembrane region constitutes a stretch of 20-30 hydrophobic amino acids. Since the amino acid sequence of EDG-1-like G protein coupled receptor is provided (SEQ ID N0: 4), one skilled in the art can easily evaluate this sequence and confirm that TM1-TM7 is, indeed, hydrophobic amino acid stretches. An amino acid sequence comparison of EDG-1-1ike G -protein coupled receptors (SEQ ID NO: 4) and EDG-1 (SEQ ID NO: 18), another G-protein coupled receptor, is also provided see original specification, Figure 4). Applicant's arguments have been fully considered but are not found persuasive. It is still not clear which amino acids comprise the transmembrane domain of SEQ ID NO: 4 so as to allow the metes and bounds of the claims to be determined. Examiner agrees that the transmembrane regions of G-protein coupled receptors are generally designated as TMI-TM7 and that each transmembrane region may comprise a stretch of 20-30 hydrophobic amino acids. The hydrophobic amino acid stretches may also be evaluated but they do not disclose where each transmembrane region specifically stars and ends. The stretches of hydrophobic amino acids contained in the receptor only disclose the general area of the potential transmembrane region. The amino acid sequence comparison of EDG-1-1ike G -protein coupled receptors (SEQ ID NO: 4) and EDG-1 (SEQ ID NO: 18) does not disclose where each transmembrane region specifically stars and ends. G -protein coupled receptors do not contain a specific transmembrane sequence present in all receptors (see Fig. 4), the sequence varies. The specification describes transmembrane regions as being designated as TM1-TM7 but

discloses no further details of said regions as they specifically pertain to instant polypeptide. Therefore for the reasons given above and in the prior Office Action the rejection is maintained.

Claims 57, 69 are newly rejected for being indefinite because it unclear when an antibody has "specificity" for the polypeptide of SEQ ID NO:4 so as to allow the metes and bounds of claim to be determined. The "specificity" of the G-protein coupled receptor has not been disclosed in the claims or the specification. When does an antibody have specificity for the polypeptide of SEQ ID NO:4 as compared to when antibody does not have specificity for the polypeptide of SEQ ID NO:4. The association or dissociation constants that determine the binding of an antibody to the substrate (polypeptide of SEQ ID NO:4) are not disclosed, therefore the metes and bounds of the claim cannot be determined.

Claims 78-81 and 83 are indefinite for depending on an indefinite claim.

Claim Rejections - 35 USC § 101 and 35 USC § 112, 1st paragraph

5. Claims 23-29, 31, 33-39, 41, 43-49, 51, 53-61, 63, 65-73, 75, 77-81 and 83 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. The amendment of claims 57 and 69 does not alter the reasons rejection of said claims as stated in the Office Action dated10/10/01.

Applicants argue the polynucleotides of the claims can be used for the diagnosis of cancer. (Original Specification, page 23, line 2.) For example, a polynucleotide sequence that is 90% identical to 30 contiguous nucleotides of SEQ ID NO:3 will hybridize to cells, tissues or classes of cells or tissues that express the EDG-I-like G protein coupled receptor. Therefore, the claimed polynucleotides certainly provide some identifiable benefit and their utility is specific and substantial under the PTO's guidelines.

Applicants arguments have been fully considered are not found persuasive. The polynucleotides of SEQ ID NO:3 has not been shown to be a marker for cancer and therefore cannot be used to support either a specific and substantial asserted utility or a well established utility.

Applicants further argue the specification states that the antagonists of the G-protein coupled receptor may be used to

treat cancer and the polynucleotides of the invention may be used for the detection of cancer. Applicants emphasize that the specification discloses at least one specific and substantial utility for the EDG-1-like G-protein coupled receptor. The use of EDG-1-1ike G-protein coupled receptor molecules to treat and/or diagnose, for example, cancer, is claimed to be a substantial utility as it provides a benefit to the public. Applicant also argues there is clearly a direct nexus between the G-protein coupled receptor (EDG-1-like) and cancer. Attention is drawn to a post-filing date publication by Van Brocklyn et al. that reports the cloning of EDG-6, a G-protein coupled receptor which has an amino acid sequence that is nearly identical to EDG-1-1ike protein

(there are only four amino acid differences at positions 78, 90, 122, and 142). Van Brocklyn implicates the G-protein coupled receptor (EDG-6) in mitogen-activated protein kinase (MAPK) signal transduction pathway. Applicant's arguments have been fully considered but are not found persuasive. Applicants' reference to post filing art cannot be used to establish utility for the claimed invention. Van Brocklyn does not disclose EDG-I-like G protein coupled receptor is a marker for cancer. At the time of filing instant Application, the specification nor prior art supported the assertion that antagonists of the EDG-I-like G protein coupled receptor could be used to treat cancer or the polynucleotides of the invention could be used for the detection of cancer. The functionality of claimed EDG-I-like G protein coupled receptor was unknown. The utilities disclosed in the specification are based on methods of using receptor polypeptides and polynucleotides as a target for diagnosis and treatment in receptor-mediated and related disorders and for drug-screening methods using receptor polypeptides and polynucleotides to identify agonists and antagonists for diagnosis and treatment. The specification discloses:

a) EBI-2 (G protein coupled receptor of SEQ ID NO:2) has about 25% identity and 49% similarity to the EBI-1 gene over an approximately 350 amino acid stretch, page 6. EDG-I-like G protein coupled receptor of SEQ ID NO:4 has about 24% identity and 73% similarity to the EDG-1 orphan G-protein coupled receptor (SEQ ID NO:18), page 6. Both EBI-1 and EDG-I-like G protein coupled receptor are found in a variety of tissue.

In light of the specification the skilled artisan can speculate that EDG-I-like G protein coupled receptor is a seven transmembrane protein belonging to the G-protein coupled receptor super family. However, no disclosure is provided within the instant specification on what specific function a putative EDG-I-like G protein coupled receptor possesses, or how to specifically assay for such, ligands that bind, promoters that activate, nor are any disease states disclosed that are directly related to EDG-I-like G protein coupled receptor dysfunction. There is no disclosure in the specification of ligands that bind to EBI-1 receptor or EDG-I-like G protein coupled receptor. The divergent nature and ligand specificity of G protein coupled receptors was disclosed in the previous Office Action (see Mudroch et al, Watson et al). The utility of EDG-I-like G protein coupled receptor cannot be implicated solely from homology to known G-protein coupled receptors because the art does not provide teaching stating that all members of a sub-family of G-protein coupled receptors must have the same effects, the same ligands and be involved in the same disease states, the art discloses evidence to the contrary. The EDG-I-like G protein coupled receptor of instant invention is considered by the examiner to be a member of the orphan receptor of G-protein coupled receptors i.e. seven transmembrane receptor with no known endogenous ligands. The specification compares claimed receptor to EDG-1 receptor of SEQ ID NO:18, which itself is an orphan receptor without a function. The receptor of SEQ ID NO:18 can not be used to infer a function on claimed EDG-I-like G protein coupled receptor because all G protein coupled receptors do not have the same function or ligand specificity . There is no

evidence of record or any line of reasoning that would support a conclusion that the claimed receptor of the instant application was, as of the filing date, useful for diagnosis, prevention, and treatment of disease, such as cancers etc. Until some actual and specific significance can be attributed to the protein SEQ ID NO:4, or the gene encoding it, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. The DNA of the instant invention and the protein encoded thereby are compounds, which share some structural similarity to receptor proteins having GPCR domains based on sequence similarity. As disclosed by the specification, the family of proteins related to EDG-1 receptor may have diverse effects and bind a diverse number of ligands. The family of proteins having GPCR like domains has different levels of expression, and play roles in the pathogenesis of various diseases. Although the family of receptor proteins having EDG receptor like domains may share some common structural motifs, various members of the family may have different sites of action and different biological effects. In the absence of knowledge of the ligand for EDG-I-like G protein coupled receptor or the biological significance of this protein, there is no immediately evident patentable use. To employ a protein of the instant invention in any of the disclosed methods would clearly be using it as the object of further research. Such a use has been determined by the courts to be a utility, which, alone, does not support patentability. The post filing art further highlights the difficulty in assigning function to G protein-coupled receptors. Brocklyn discloses the EDG family of proteins is expressed in various tissues, have different ligand specificity

and have different activities. EDG-1, EDG-3, and EDG-5 are spingosine-1-phospahte (SPP) receptors; EDG-2 and EDG-4 and EDG-7 are lysophosphatidic (LPPA) receptors. Brocklyn discloses before their publication (2000) it was unknown that EDG-6 was a receptor for SPP. Brocklyn also discloses that EDG-6 does not belong to either SPP or LPA subfamily of EDG receptors but it displays a similar degree of homology to all 5 of the previously identified members of the family. Therefore, Brocklyn argues away from prediction function based on homology to known proteins in a family.

In conclusion, the utilities asserted by Applicant are not specific or substantial. Since no specific function of the polypeptide of instant invention is known, and the hypothesized function is based entirely on conjecture from homologous polypeptides, the asserted utilities are not specific to instant polypeptide, but rather are based on family attributes. Neither the specification nor the art of record disclose the protein of SEQ ID NO:4 or fragments thereof useful to identify drugs that affect said protein and modulate its activity. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed receptor and fragments thereof, further experimentation is necessary to attribute a utility to the claimed polypeptides and fragments thereof.

6. Claims 23-29, 31, 33-39, 41, 43-49, 51, 53-61, 63, 65-73, 75, 77-81 and 83 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted

utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the EDG-I-like G protein coupled receptor and fragments thereof, further experimentation is necessary to attribute a utility to the EDG-I-like G protein coupled receptor polynucleotides encoding said receptors.

Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Applicant argues the rejection under 35 U.S.C. 112, first paragraph be withdrawn because the polynucleotides have utility. Applicants' arguments have been fully considered but are not found persuasive. The claims lack utility for the reasons given above and in the previous Office Action, therefore the rejection is maintained.

7. Claims 23-29, 31, 33-39, 41, 43-49, 51, 53-61, 63, 65-73, 75, 77-81, 83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue the present claims recite generic formulae that indicate with specificity the subject matter that the claims encompass. Applicants argue they show the complete sequence of EDG-1-like G-protein coupled receptor, and that polynucleotides at least 90% identical to the specific polynucleotide sequence will show activity. Applicants' arguments have been fully considered but not found persuasive. There is no description of the conserved regions, which are critical to the structure, and function of the genus claimed. The specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of polypeptides and how they relate to function. The activity and ligand that bind to specific regions of the receptor are not disclosed. The claimed genus of polynucleotides encompasses billions of polynuclotides encoding billions of receptors, all with no known function or assayable activity. The specification discloses the polynucleotide of SEQ IUD NO:3 encoding the protein of SEQ ID NO:4. The claims encompass billions and billions polynucleotides encoding proteins which are structurally and functionally unrelated to the protein of SEQ ID NO:4. Claims 23-29, 31, 33-39, 41, 43-49, 51, 53-61, 63, 65-73, 75, 77-81, 83 are rejected for reasons of record (1/10/01) and those given above.

Therefore only the use of isolated polynucleotide, SEQ ID NO:3, encoding the polypeptide shown in SEQ ID NO:4, meets the written description provision of 35 USC 112, first paragraph.

No claim is allowed.

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GARY KUNZ
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Nirmal s. Basi
Art unit 1646
June 28, 2004